REMARKS

Claims 17 and 25-33 are pending in the instant application. Claim 17 has been amended. Support for the amendments to claim 17 may be found in the specification, for example, at p. 15, l. 27-28; Example 4, in particular p. 24 l. 30-31; and p. 12, l. 15-17 which clearly states that granzyme B can be the only pharmaceutically active component in the composition. Claim 29 has been amended for the sake of clarity in order to recite the analysis of the cells affected by infection or inflammation or tumor cells for surface expression of Hsp70 as a separate step (a).

In the Office Action mailed March 21, 2008, the Examiner rejected the claims as follows:

1. Double patenting;
2. Claims 17, 28 and 29 are rejected under 35 U.S.C. §102(b) as being anticipated by TROUET I (WO 01/91798);
3. Claims 17, 28 and 29 are rejected under 35 U.S.C. §102(e) as being anticipated by TROUET II (20040014652); and
4. Claims 17 and 25-23 are rejected under 35 U.S.C. §103(a) as being obvious over TROUET I or II.

Each rejection is addressed below.

1. Double patenting.

The amendment to Claim 29 should obviate any potential double patenting rejection of claims 29-33 over claims 17 and 25-28.

2. The claims are novel.

Claims 17 and 28 are rejected under 35 U.S.C. §102(b) as being anticipated by TROUET I (WO 01/91798) and under 35 U.S.C. §102(e) as being anticipated by TROUET II (20040014652). The disclosure of these two references is identical so the rejections are considered together. A claim is anticipated only if "each and every element as set forth in the claims is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. Of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Claim 17 as amended is distinguished over TROUET I and II as claim 17 now specifies that the pharmaceutical composition consists essentially of granzyme B. Applicants submit that

this amendment excludes the prodrug form of granzyme B, which, in addition to the functional granzyme B sequence comprises a transport peptide. A composition consisting essentially of granzyme B would not include the transport peptide. Claim 29 as amended which now more clearly specifies the step of (a) analyzing target cells of a patient for surface expression of Hsp70 is also clearly distinguished over TROUET I and II. This step is not taught by TROUET I or II.

With respect to Claim 17 (and previous) Claim 29 and the Examiner's comments in the paragraph bridging pages 2 and 3 of the Office Action concerning the role of the transport peptide of the granzyme B prodrug taught in TROUET I and II, it is clear from the description of the instant application as filed at page 12, lines 3 to 23 that the absence of "further pharmaceutically active ingredients" is meant to exclude transport peptides. This feature is based on the observation in accordance with the present invention that the effective treatment of **Hsp70 membrane positive tumors** with isolated granyzme B does not require perforin to allow granzyme B to reach the cytoplasm and the nucleus of the tumor cells or any other transport peptide, since the uptake of granzyme B is mediated via Hsp70:

> "The invention also relates to the use of granzyme B for the preparation of a pharmaceutical composition for the perforin-independent treatment of tumors, viral or bacterial infections or inflammatory diseases.
>
> A most important aspect of the present invention is mirrored by the above recited embodiment. In contrast to the speculation of the prior art, it could be shown in accordance with the present invention, that granzyme B is effective in the treatment of tumors independent of the perforin-pathway. This has important applications in the strategy of treating tumors since uptake of the pharmaceutically active compound may now be deviced independent of the perforin-pathway. ...
>
> In a preferred embodiment of the use of the present invention, granzyme B is used as the only pharmaceutically active component in said pharmaceutical composition.
>
> Again, this preferred embodiment of the invention has important implications in the design of the necessary components of the pharmaceutical composition to be used in the treatment of cancers. Importantly, there is no need to include further pharmaceutically active ingredients into the pharmaceutical composition in order to effectively treat tumors and/or reduce the size of the tumors or to treat viral or bacterial infections or inflammatory diseases" (emphasis added).

Thus, the application as filed clearly teaches that perforin and equivalent transport or signal peptides are excluded from the pharmaceutical composition to be administered in accordance with Claims 17 and 29.

Furthermore, the Examiner is wrong when stating that step (b) of claim 17 and previous step (b), now step (c) of Claims 17 and 29 cannot be controlled by the administration of the drug. In fact, this is the very teaching of TROUET I and II to control the delivery of granzyme B by the use of a transport peptide in the formulation of a granzyme B prodrug. Thus, in accordance with TROUET I and II, granzyme B enters the target cell by and together with the transport peptide; see TROUET II in paragraphs [122] and [123] at page 11. Due to this measure granzyme B delivery into the cell is controlled and does not allow granzyme B entering the cells via ion channels formed by Hsp70. For this reason, the limitation of step (b) of Claim 17, and step (c) of amended Claim 29, is not fulfilled.

For the foregoing reasons, Applicants respectfully submit that the claims are not anticipated by TROUET I or II and request that the corresponding rejections be withdrawn.

4. The claims are not obvious.

Claims 17 and 25-28 are rejected under 35 U.S.C. §103(a) as being obvious over TROUET I or II. A *prima facie* case of obviousness requires the Examiner to cite a combination of references which (a) disclose the elements of the claimed invention, (b) suggests or motivates one of skill in the art to combine those elements to yield the claimed combination, and (c) provides a reasonable expectation of success should the claimed combination be carried out. Failure to establish any one of the these three requirements precludes a finding of a *prima facie* case of obviousness, and, without more, entitles Applicant to allowance of the claims in issue.[1] In addressing this rejection, Applicants focus on the independent claims since non-obviousness of an independent claim necessarily leads to non-obviousness of claims dependent therefrom.[2]

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1 *See, e.g., Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990).

2 §MPEP 2143.03.

In the present case, any *prima facie* case of obviousness established by the Examiner is now rebutted by the amendments to the claims. In particular, TROUET I and II do not teach or suggest the following claim elements:

Claim 17: pharmaceutical composition consisting essentially of isolated granzyme B; and allowing granzyme B to enter said cells via Hsp70 on the cell surface

Claim 29: analyzing target cells of a patient for surface expression of Hsp70; and allowing granzyme B to enter said cells via Hsp70 on the cell surface

Thus, since the cited references do not teach each element of the claims the claims are not obvious in view of TROUET I and II.

Moreover, it is clear that the present inventors have proceeded contrary to the accepted wisdom in the art. See MPEP(x)(D)(3). This in itself is strong evidence of nonobviousness. The accepted wisdom in the art, as evidenced by TROUET I and II, is that granzyme B in its mature form **cannot** be taken up by cells; instead, perforin or a transport peptide is required to enable granzyme B to traverse the cell membrane. In this respect, the Examiner's attention is respectfully directed to paragraphs [140] and [141] at page 13 of TROUET II, corresponding to TROUET I at page 31, line 28 to page 32, line 11:

> "Granzyme B, a single-chain serine protease of about 28.5 kDa, was first demonstrated to play a crucial role in the initiation of apoptosis induced by killer lymphocytes. This killing effect results from the synergistic effect of perforin, a membranolytic protein and the serine protease granzyme B (Blink et al., 1999, Immunol. Cell Biol. 77: 206-215; Trapani et al., 1998, J. Biol. Chem. 273: 27934-27938). *Perforin allows granzyme B to reach the cytoplasm and the nucleus of cells by inducing the formation of transmembrane pores that constitute a passage for the enzyme*. Granzyme B then induces apoptosis by starting pre-existing death pathways through the enzymatic cleavage and activation of pro-caspases, and also by directly cleaving nuclear substrates such as DNA-PK and poly-ADP ribosepolymerase (Froelich et al., 1996, Biochem. Biophys. Res. Commun. 227: 658-665; Yang et al., 1998, J. Biol. Chem. 273: 34278-34283). *In the prodrug, the transport peptide potentially plays the role of perforin by allowing granzyme B to enter the cell and to induce apoptosis.*

> Preferred prodrugs of this embodiment of the present invention comprise granzyme B *linked to the PEG-Ala-Leu-Ala-Leu derivative of the transport peptide*, described above, via an amide bond from the carboxy terminus of granzyme B to the amino terminus of the derivatized transport peptide. *The granzyme B prodrug can be administered* alone or in combination with doxorubicin or any doxorubicin prodrug described above" (emphasis added).

The cited paragraphs clearly indicate that TROUET I and II teach **administration of granzyme B in a prodrug form** and in conjunction with a transport peptide, rather than administration of isolated granzyme B as required in the pending claims. Thus, contrary to the Examiner's assertion in the aforementioned paragraph of the Office Action the manufacture of a granzyme B prodrug as taught in TROUET I and II cannot be equated with the administration of isolated granzyme B. In fact, this feature is one advantage of the present invention over the prior art, i.e. that laborious modification of granzyme B is not required. Furthermore, as already discussed before, TROUET I and II do NOT allow granzyme B to enter the cells via Hsp70 on the cell surface but through and with the transport peptide.

Besides the above discussed features which clearly distinguish the claimed invention from the prior art, it also emphasized that the method of treatment in accordance with the present invention provides an important advantage over the approach taught in TROUET I and II. First of all, the transport peptide used by TROUET to let granzyme B traverse the cell membrane does not distinguish between tumor cells and healthy cells Rather, with respect to tumor specificity TROUET relies on the presence of higher concentrations of cleaving peptidases in tumor cells and endothelial cells involved in tumor angiogenesis compared to healthy cells, the peptidase mediated cleavage of the prodrug resulting in the release of the transport peptide – drug; see, e.g., TROUET I at page 2, lines 17 to 25 and page 4, line 26 to page 5, line 9. However, as admitted by TROUET the peptidases are not unique to tumors or tumor cells; see, e.g., TROUET I at page 2, line 26 to page 3, line 1. Thus, the approach of TROUET is at serious risk to affect healthy cells as well, particularly normal dividing cells in the process of wound healing where the tumor destroyed a healthy organ or tissue, and where the secretion of peptidases represents a common response of the body.

In contrast, the present application in Example 4 and Figure 3 demonstrates that the method of the present invention selectively induces apoptosis by granzyme B in Hsp70 membrane-positive tumor cells while Hsp70 membrane-negative cells remain unaffected. Since the presence of Hsp70 on the cell membrane is unique to tumor cells and healthy cells can be reliable proven to be Hsp70 membrane-negative, there is substantially no risk of severe side effects, contrary to the approach of TROUET. Hence, the present invention provides a safe therapeutic use of granzyme B for the specific treatment of tumors as well as other diseased cells which are characterized by the presence of Hsp70 on their cell surface membrane.

For the foregoing reasons, Applicants respectfully request that the obviousness rejections be withdrawn.

Conclusion

The Applicant believes the arguments set forth above traverse the Examiner's rejections and therefore request these alleged grounds for objection and rejection be withdrawn. Should the Examiner believe a telephone interview would aid in the prosecution of this application, the Applicant encourages the Examiner to call the undersigned collect.

Dated: July 14, 2008

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